## REMARKS

### Claim Amendements

Claims 1 and 31 are currently pending herein. Claim 1 has been amend to clarify that which Applicants regard as the invention. New Claims 148-149 have been added herein. Support for the amendments to Claim 1 and new Claims 148-149 can be found throughout the specification. No new matter has been added.

### Rejoinder

Applicants believe that Claims 1 and 31 are in condition for allowance and, therefore, respectfully request that withdrawn Claims 3, 5, 10-16, 18, 32, 40, 42, 95, 99 and 147-149 be rejoined.

### Interview

Applicants would like to thank Examiner Hill for taking the time to have the telephonic interview on November 24, 2008. Claim 1 has been amended herein to reflect the discussion during the interview and to clarify the claimed invention.

### Rejection of Claims 1 and 31 Under requirements of 35 U.S.C. §103(a)

Claims 1 and 31 are rejected under 35 U.S.C. §103(a) as being unpatentable over Kandimalla, Kandimalla and Simmonds.

Applicants respectfully disagree that the cited art teaches or suggests an oligonucleotide comprising the instantly claimed RpG dinucleotide, or the linking of two such oligonucleotides via a non-nucleotidic linker. Furthermore, Applicants disagree with the Office Action's characterization of the cited art and the alleged motivation to combine the cited art to reach the instantly claimed compound.

As stated in Applicants previous Response to this Office Action (submitted on August 21, 2008), which is incorporated herein by reference, the Office Action fails to explain how one skilled in the art would either be motivated to try, or have a reasonable expectation of success with this "simple" substitution considering Kandimalla (2001) teaches that a YpG-containing oligonucleotide in which Y was deoxy-P-base nucleoside showed **little or no immunostimulatory activity** (see page 809, column 2, lines 22-24)(emphasis added).

In an attempt to justify the rejection, the Office Action's main points are as follows:

1. "Kandimalla et al (2001) teach the simple substitution of an unmethulated cytosine for cytosine analogues that are isostructural with natural cytosine, including a P-base, thereby demonstrating that substituting cytosine for a P-base in an oligonucleotide that is to be assayed for immunostimulatory activity is routine."

2. while Kandimalla et al (2001) teach only one species of a P-base cytosine analogue, those of ordinary skill in the art (Simmonds et al) recognize the existence of a genus of P-base cytosine analogues, including the instantly claimed analogue illustrated in Figure 24 of the instant application. It was well within the skills of the ordinary artisan to substitute a first P-base cytosine analogue for a second P-base cytosine analogue."

and

3.

Thus, the result yielded by the analogue 7 P-base does not clearly and absolutely teach away from all other species within the genus of P-base cytosine analogues (Applicant's argument) because Applicant clearly teaches that other species of similar structure should be tested as there are other isostructural cytosine analogue species from which the ordinary artisan may reasonably expect (at least 40% probability of success, as per 2/5 of the monocyclic cytosine analogues) to detect immunostimulatory activity when assayed under the appropriate conditions. Thus, at the time of the invention, those of ordinary skill in the art had both taught, suggested and possessed a reasonable expectation of success that a P-base would function as a cytosine substitute (C*) in an immunostimulatory oligonucleotide comprising a C*pG motif.

With respect to 1), the Office Action's comments regarding obviousness merely amount to an assertion that one of ordinary skill in the art would have been able to arrive at the Applicants' invention because he had the necessary skills to carry out the requisite steps. There must, however, still be prior art that suggests the claimed invention in order for a prima facie case of obviousness to be made out. The Office Action fails to provide any such motivation, but rather merely identifies claimed elements within the prior art. A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be

carried out (See *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995)). That which is within the capabilities of one skilled in the art is not synonymous with obviousness.

Points 2) and 3) fail to provide the teachings that 1) lacks.

With respect to 2), Applicants do not agree with the Office Action's creation of a genus of P-base cytosine analogues, and that P-base and the instantly claimed R group are species thereof. Rather, a pyrrolo base is different from a P-base. However, even if there were such a genus of cytosine analogues, the mere existence of this genus would not render the instantly claimed compound obvious. As noted above, there must be prior art that suggests the claimed invention in order for a prima facie case of obviousness to be made out.

Again the Office Action fails to identify any teaching or suggestion within the prior art to obtain the instantly claimed invention. Applicants have stated on numerous occasions that Simmonds only teaches various base analogs and states that these analogs may be incorporated into nucleic acids and oligonucleotides. Simmonds goes on to state that these analogs have potential for Watson-Crick base pairing with a native base or base analog.

The PTO questions whether Applicants have provided evidence that the claimed compounds do not molecularly act with its target through hydrogen bonds. However, this is not what the Applicants are suggesting. Rather, Applicants are pointing out that Simmonds fails to provide any teaching or suggestion to incorporate these base analogues into the CpG dinucleotide, or whether those analogues would still be recognized by the TLR9 receptor, and as such, is irrelevant to the instant invention. So, even though the mechanism of action of the CG dinucleotide in an oligonucleotide-based immunostimulatory compound was not well understood at the time the present invention was made, it certainly could not be by Watson-Crick base-pairing, since the target is a protein, TLR9, and not a nucleic acid. There remains absolutely no evidence of record, and Applicants are aware of none in the prior art, to suggest that one skilled in the art of oligonucleotide-based immunostimulatory compounds would have considered the instantly claimed R to be a functional alternative to cytosine in the context of the CG dinucleotide, nor to suggest that such a substituted compound would have immunostimulatory activity. This is further supported in response to point 3) below.

With respect to 3), Applicants do not understand how the Office Action can state that at the time of the invention, one of ordinary skill in the art taught, suggested and possessed a reasonable expectation of success that a P-base would function as a cytosine substitute (C*) in an

immunostimulatory oligonucleotide comprising a C*pG motif. This statement blatantly ignores the fact that, at the time of the invention, those of ordinary skill in the art **knew** that P-base **would not** function as a cytosine substitute (C*) in an immunostimulatory oligonucleotide comprising a C*pG motif.

As stated above, Kandimalla (2001) teaches that a YpG-containing oligonucleotide in which Y was deoxy-P-base nucleoside showed little or no immunostimulatory activity. Furthermore, as noted in a 132 Declaration by Dr. Kandimalla, the CG-containing oligonucleotide having a deoxy-P-base modification at the C position (of the CG dinucleotide) was an inactive molecule and that the phrase "showed little or no immunostimulatory activity" meant that those modifications did not work.

The PTO cannot ignore these teachings of Kandimalla as the full scope and content of the prior art must be considered for obviousness. Thus, Kandimalla (2001) demonstrates what one of ordinary skill in the art actually taught, suggested and possessed with regards to a P-base substitution for cytosine in the CpG motif. Stated another way, Kandimalla (2001) teaches away from the use of bicyclic purines as that motif abolished the immunostimulatory activity of the CG dinucleotide. Consequently, a CG-containing oligonucleotide having the instantly claimed modification which results in a functional molecule cannot be an obvious variant of a deoxy-P-base modification which resulted in a non-functioning molecule.

The PTO attempts to overcome this deficiency by characterizing Kandimalla (2001) as demonstrating that at least a 40% probability of success for monocyclic cytosine analogues would provide the motivation with reasonable expectation of success for bicyclic cytosine analogues despite the fact that 100% of the bicyclic analogues tested didn't work. However, this overly simplified comparison by the PTO is unsupported by any evidence of record and it ignores whether there would be any functional differences between monocyclic and bicyclic analogues in the CG dinucleotide. Moreover, as stated by the Office Action, that both P-base and the analogue described in Simmonds share hydrogen bond acceptor and donor atoms on the same face only further supports that one skilled in the art would not have been motivated to use the instantly claimed R in the CpG motif since P-base didn't work.

As Kandimalla (2001) teaches that some modifications to the C of the CpG motif can abolish activity and, more importantly that modification of the C of the CpG motif with a bicyclic cytosine (P-base) abolished the activity, one skilled in the art would not have been

motivated, with a reasonable expectation of success, to use the instantly claimed R group in the CpG motif. The Office Action fails to overcome this deficiency. Therefore, Claims 1 and 31 are patentable over Kandimalla, Kandimalla and Simmonds.

**Provisional obviousness-type double patenting**

Claims 1 and 31 are provisionally rejected over various claims of copending Application Nos. 10/361,111; 10/865,245; 10/925,873; 11/153,054; and 11/174,002.

As stated by the Examiner, this is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Please note that, with regards to patent term, U.S. Application Nos. 10/361,111; 10/865,245; 10/925,873; 11/153,054; and 11/174,002 are the later filed applications.

Therefore, if this provisional double patenting rejection is the only remaining rejection in the application, Applicants request that the Examiner withdraw the rejection in the instant [earlier filed] application thereby permitting this application to issue without need of a terminal disclaimer. (See MPEP §804(I)(B)). Applicants will then consider filing a Terminal Disclaimer or take any other action deemed necessary in the later filed, copending applications.

Claims 1 and 31 are provisionally rejected over various claims of copending Application Nos. 10/694,383 and 10/694,586 in view of Simmonds.

Applicants respectfully disagree. As stated above, the cited art fails to teach or suggests an oligonucleotide comprising the instantly claimed RpG dinucleotide, or the linking of two such oligonucleotides via a non-nucleotidic linker.

Furthermore, as discussed above, this rejection continues to ignore the fact that, at the time of the invention, those of ordinary skill in the art **knew** that P-base **would not** function as a cytosine substitute (C*) in an immunostimulatory oligonucleotide comprising a C*pG motif. Applicants have pointed out that Kandimalla (2001) teaches a YpG-containing oligonucleotide in which Y was deoxy-P-base nucleoside showed little or no immunostimulatory activity. Applicants are aware that Kandimalla (2001) is not part of the rejection. However, the PTO cannot disregard the teachings of Kandimalla regardless of whether it is officially part of the rejection. The full scope and content of the prior art must be considered for obviousness and not just what is cited in the rejection.

Thus, Kandimalla (2001) is being pointed out to demonstrate what one of ordinary skill in the art actually taught, suggested and possessed with regards to a P-base substitution for cytosine in the CpG motif. Furthermore, the structural similarity between P-base and the cytosine analogues described in Simmonds further supports that one skilled in the art would not have been motivated, with a reasonable expectation of success, to modify the CpG motif with the instantly claimed R group. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 1 and 31 are provisionally rejected over various claims of U.S. Patent No. 7,276,489.

Applicants respectfully disagree. As stated above, the cited art fails to teach or suggests an oligonucleotide comprising the instantly claimed RpG dinucleotide, or the linking of two such oligonucleotides via a non-nucleotidic linker.

Furthermore, as discussed above, this rejection continues to ignore the fact that, at the time of the invention, those of ordinary skill in the art **knew** that P-base **would not** function as a cytosine substitute (C*) in an immunostimulatory oligonucleotide comprising a C*pG motif. Applicants have pointed out that Kandimalla (2001) teaches a YpG-containing oligonucleotide in which Y was deoxy-P-base nucleoside showed little or no immunostimulatory activity. Applicants are aware that Kandimalla (2001) is not part of the rejection. However, the PTO cannot disregard the teachings of Kandimalla regardless of whether it is officially part of the rejection. The full scope and content of the prior art must be considered for obviousness and not just what is cited in the rejection.

Thus, Kandimalla (2001) is being pointed out to demonstrate what one of ordinary skill in the art actually taught, suggested and possessed with regards to a P-base substitution for cytosine in the CpG motif. Furthermore, the structural similarity between P-base and the cytosine analogues described in Simmonds further supports that one skilled in the art would not have been motivated, with a reasonable expectation of success, to modify the CpG motif with the instantly claimed R group. Reconsideration and withdrawal of the rejection is respectfully requested.

## CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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